Trial Forge: working together to make trials more efficient

Shaun Treweek

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streweek@mac.com

Health Services Research Unit
University of Aberdeen

HSRU is funded by the Chief Scientist Office of the Scottish Government Health Directorates. The author accepts full responsibility for this talk.

R. Aber Vrach
Lanilis
R. Aber Benoit
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Let’s do what we did last time..

‘There is a peculiar paradox that exists in trial execution - we perform clinical trials to generate evidence to improve patient outcomes; however, we conduct clinical trials like anecdotal medicine:

- **we do what we think works**
- **we rely on experience and judgement and..**
- **limited data to support best practices.’**

Monica Shah in ‘Site selection in global clinical trials in patients hospitalized for heart failure: perceived problems and potential solutions’. Heart Failure Review 2014; 19:135-52.

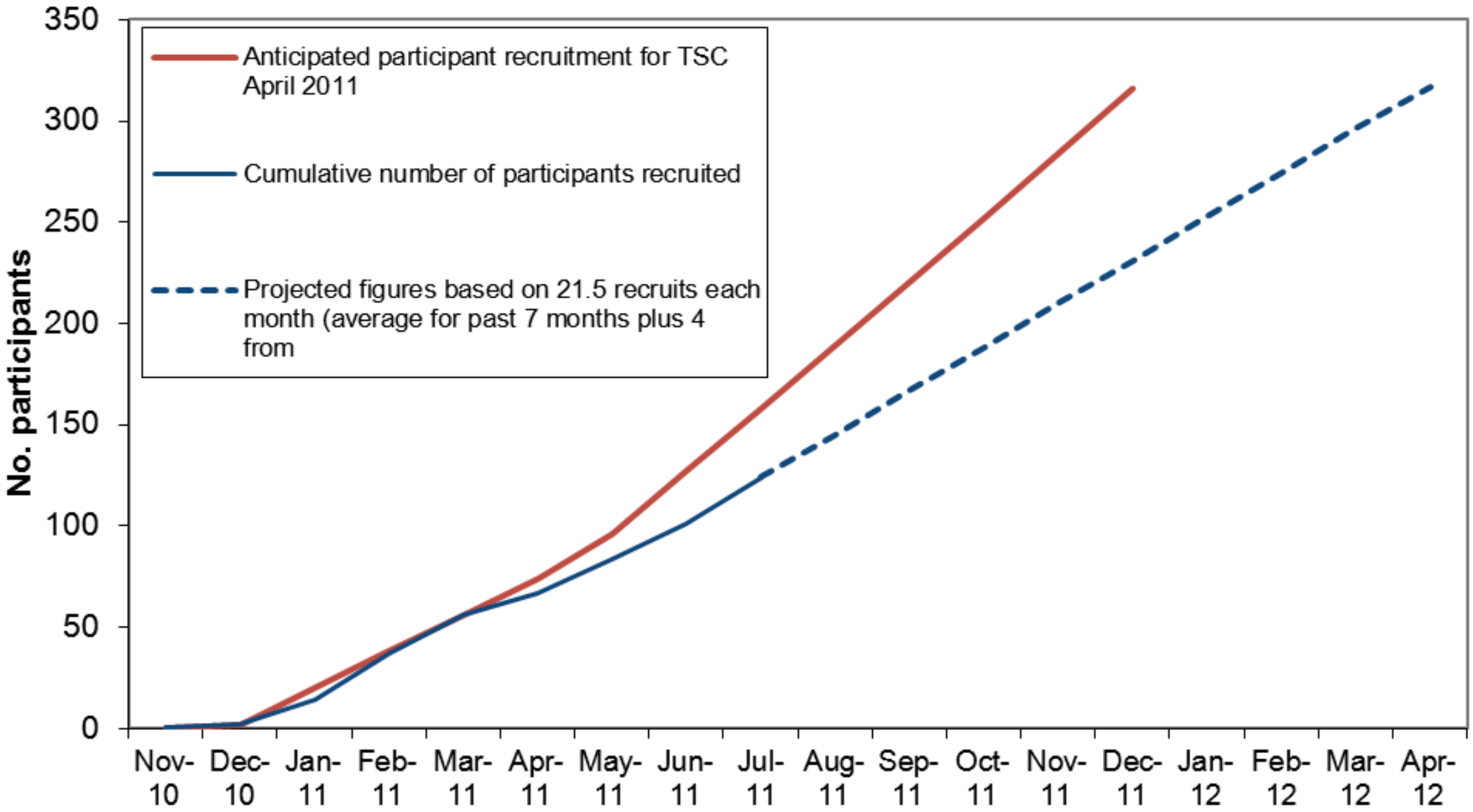
And there's more..

The way we design a trial often makes it hard to:

- **do the trial**
- **convince others, especially those we hope will use the results, that those results are relevant**

Example 1: participants

A strangely familiar graph..



What helps recruitment?

Strategies to improve recruitment to randomised controlled trials (Review)

Treweek S, Mitchell E, Pitkethly M, Cook J, Kjeldstrøm M, Johansen M, Taskila TK, Sullivan F, Wilson S, Jackson C, Jones R, Lockhart P

THE COCHRANE COLLABORATION®

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3 things

THE COCHRANE COLLABORATION®

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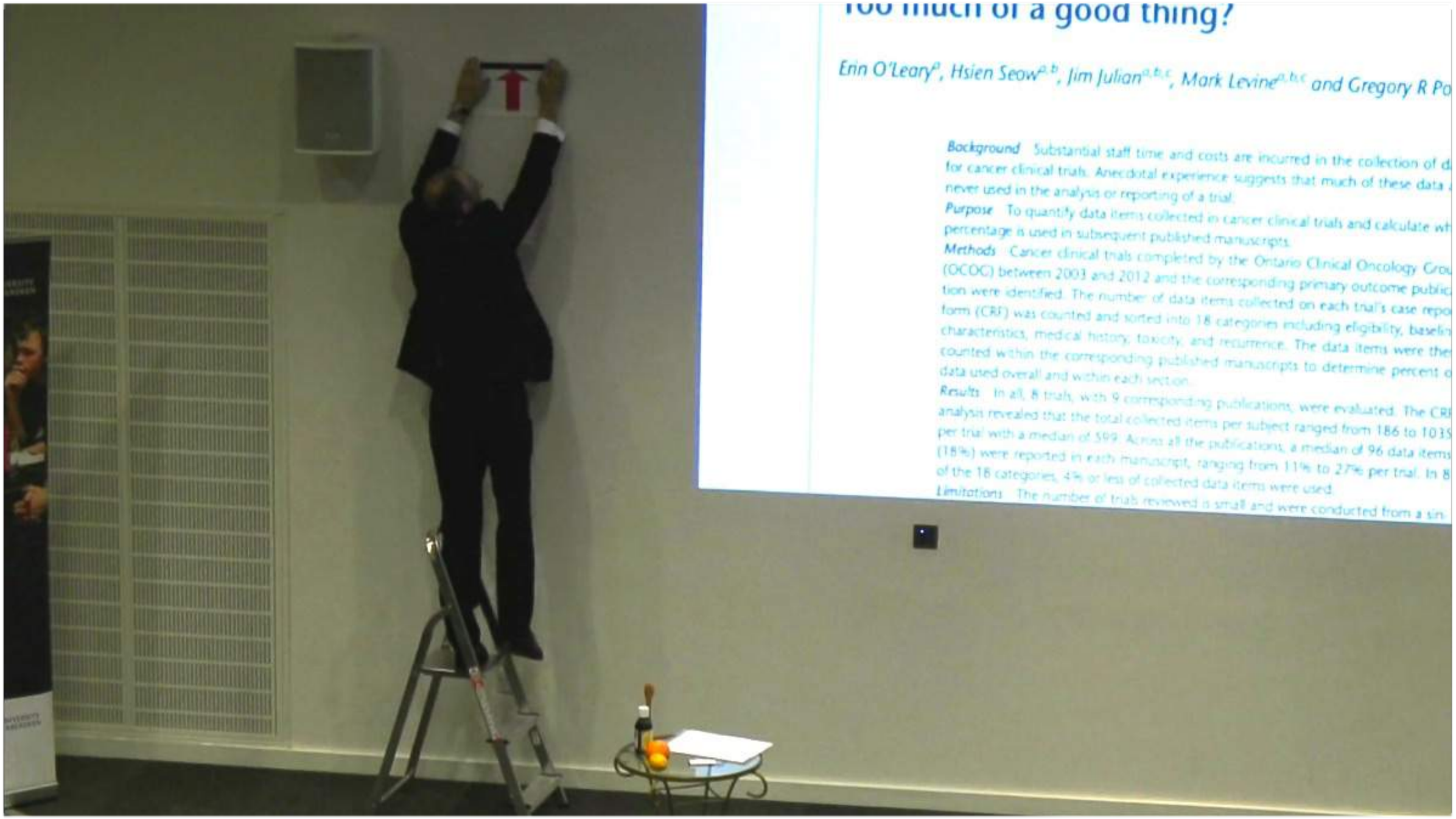
THE COCHRANE COLLABORATION®

Example 2: data collection



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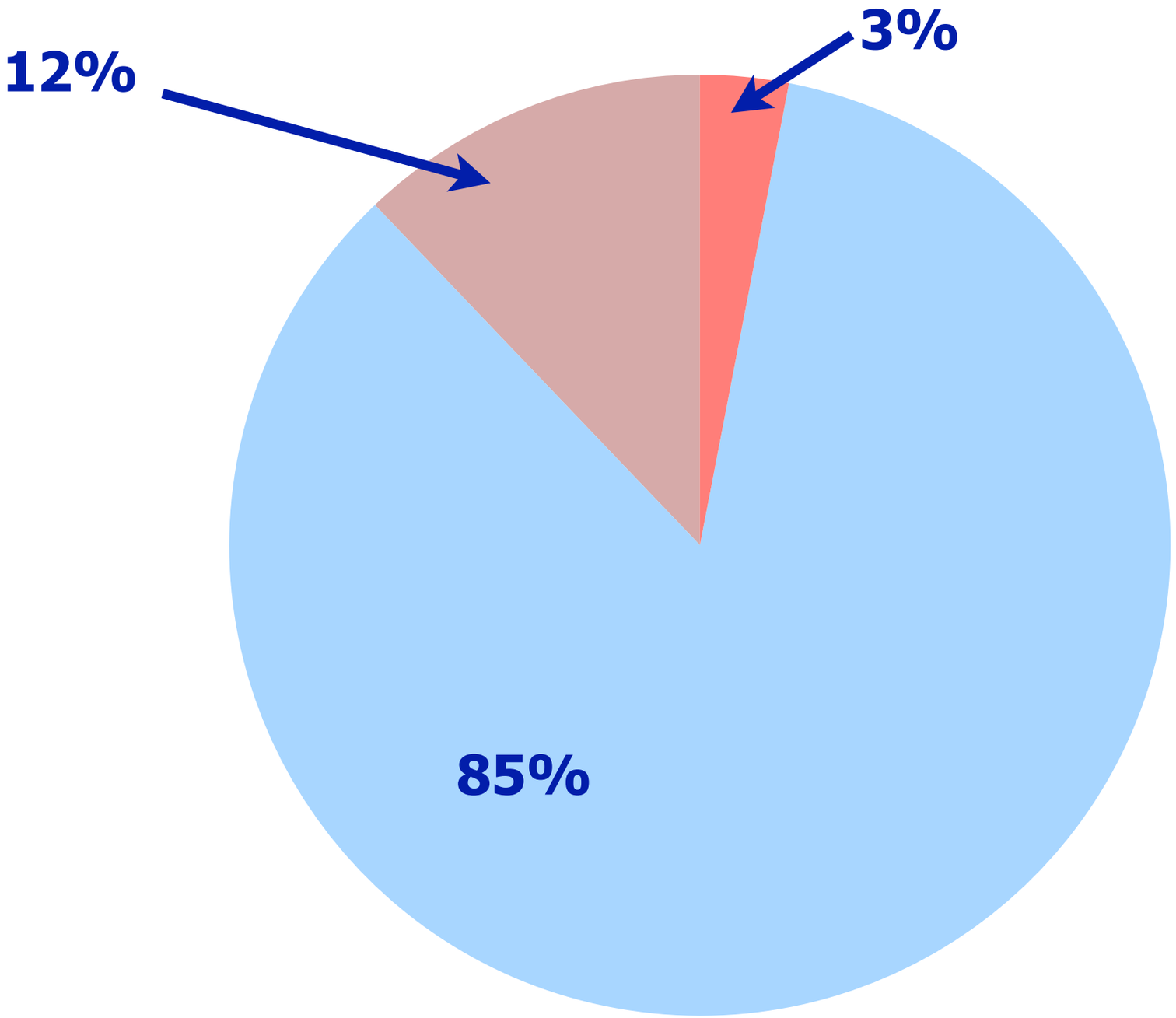

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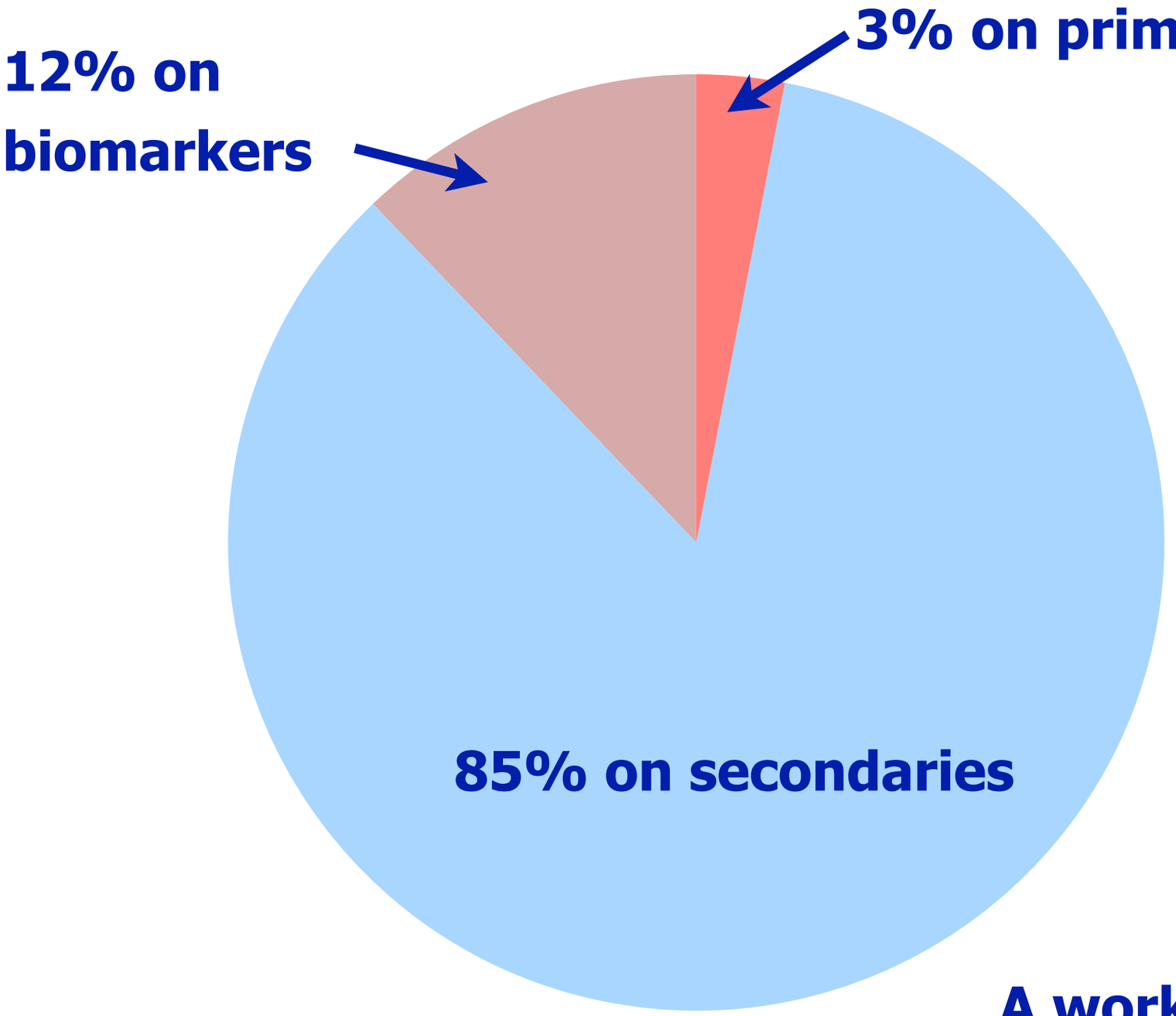

Primary = 81 hrs

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Secondaries = 2265 hrs

Total = 2670 hrs

A working year is about 1725 hrs

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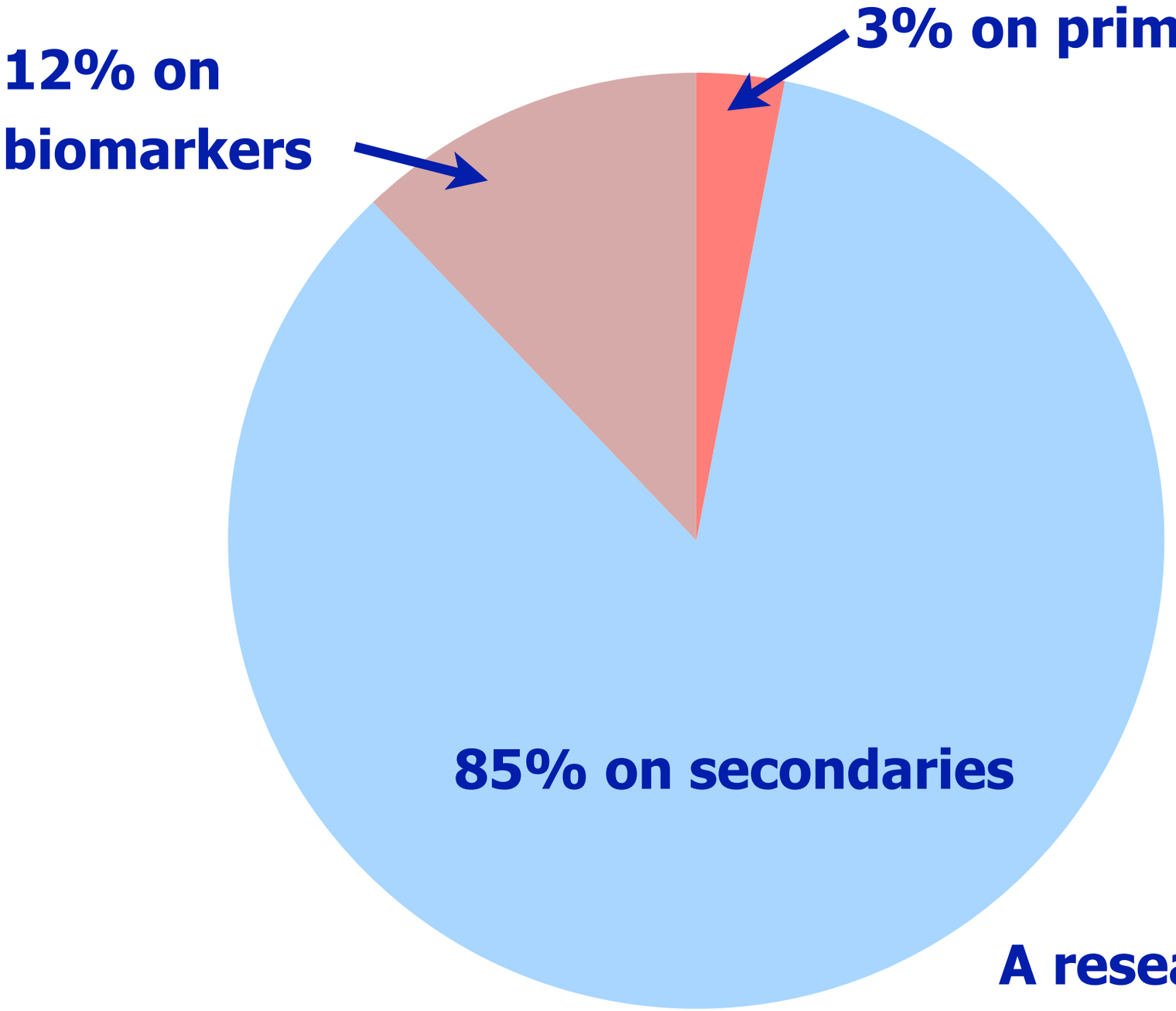

Primary = £2,106

Biomarker = £8,424

Secondaries = £58,890

Total = £69,420

A research nurse costs around £26 per hour

But we collect so much data..

CLINICAL TRIALS

DATA MANAGEMENT AND TRIAL CONDUCT

Clinical Trials 2013; **10**: 624–632

Data collection in cancer clinical trials: Too much of a good thing?

Erin O'Leary[a], Hsien Seow[a,b], Jim Julian[a,b,c], Mark Levine[a,b,c] and Gregory R Pond[a,b,c]

Background Substantial staff time and costs are incurred in the collection of data for cancer clinical trials. Anecdotal experience suggests that much of these data are never used in the analysis or reporting of a trial.

Purpose To quantify data items collected in cancer clinical trials and calculate what percentage is used in subsequent published manuscripts.

Methods Cancer clinical trials completed by the Ontario Clinical Oncology Group (OCOG) between 2003 and 2012 and the corresponding primary outcome publication were identified. The number of data items collected on each trial's case report form (CRF) was counted and sorted into 18 categories including eligibility, baseline characteristics, medical history, toxicity, and recurrence. The data items were then counted within the corresponding published manuscripts to determine percent of data used overall and within each section.

Results In all, 8 trials, with 9 corresponding publications, were evaluated. The CRF analysis revealed that the total collected items per subject ranged from 186 to 1035

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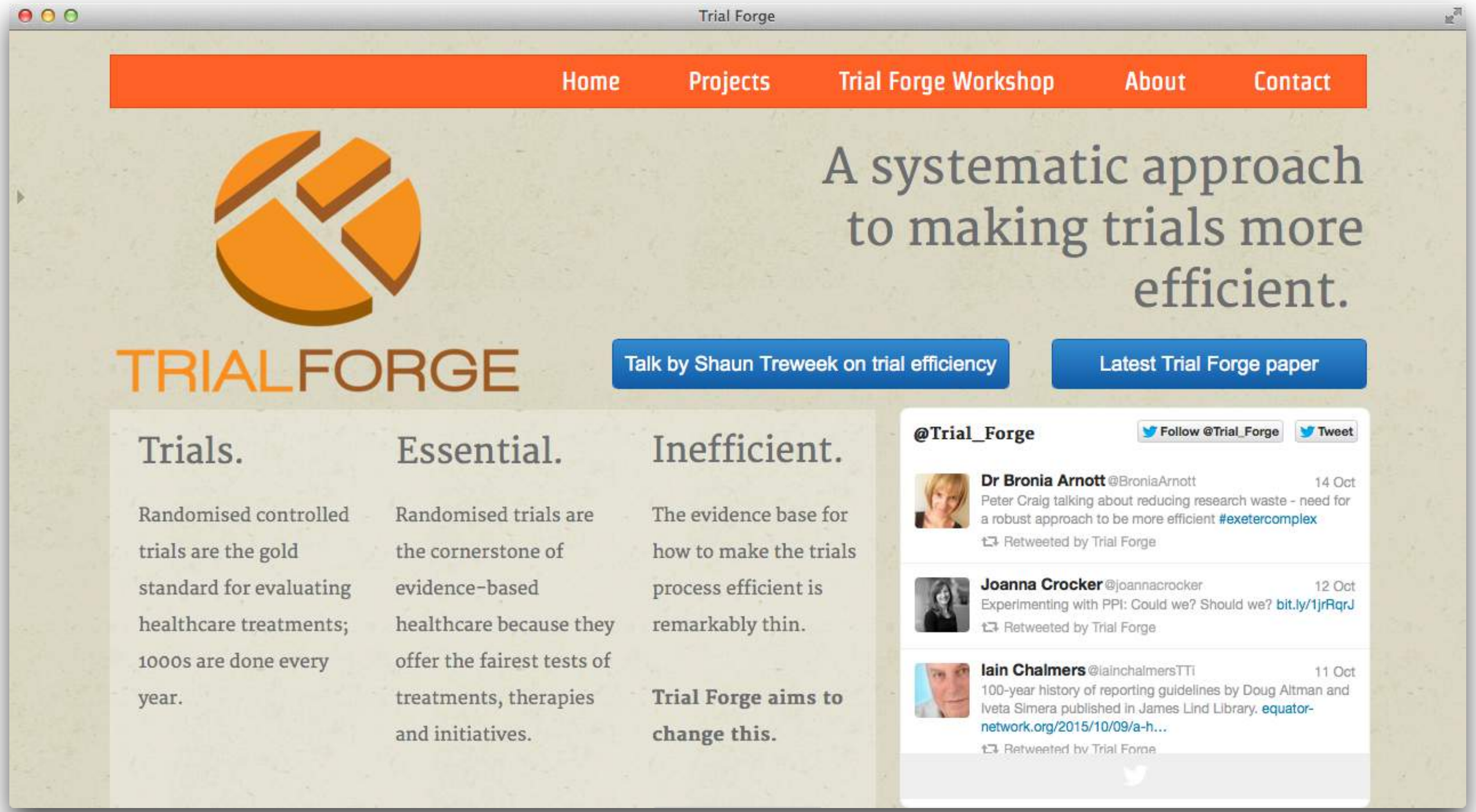
So, what to do?


Trial Forge
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A systematic approach to making trials more efficient.
TRIALFORGE
Talk by Shaun Treweek on trial efficiency
Latest Trial Forge paper
Trials.
Randomised controlled trials are the gold standard for evaluating healthcare treatments; 1000s are done every year.
Essential.
Randomised trials are the cornerstone of evidence-based healthcare because they offer the fairest tests of treatments, therapies and initiatives.
Inefficient.
The evidence base for how to make the trials process efficient is remarkably thin.
Trial Forge aims to change this.
@Trial_Forge
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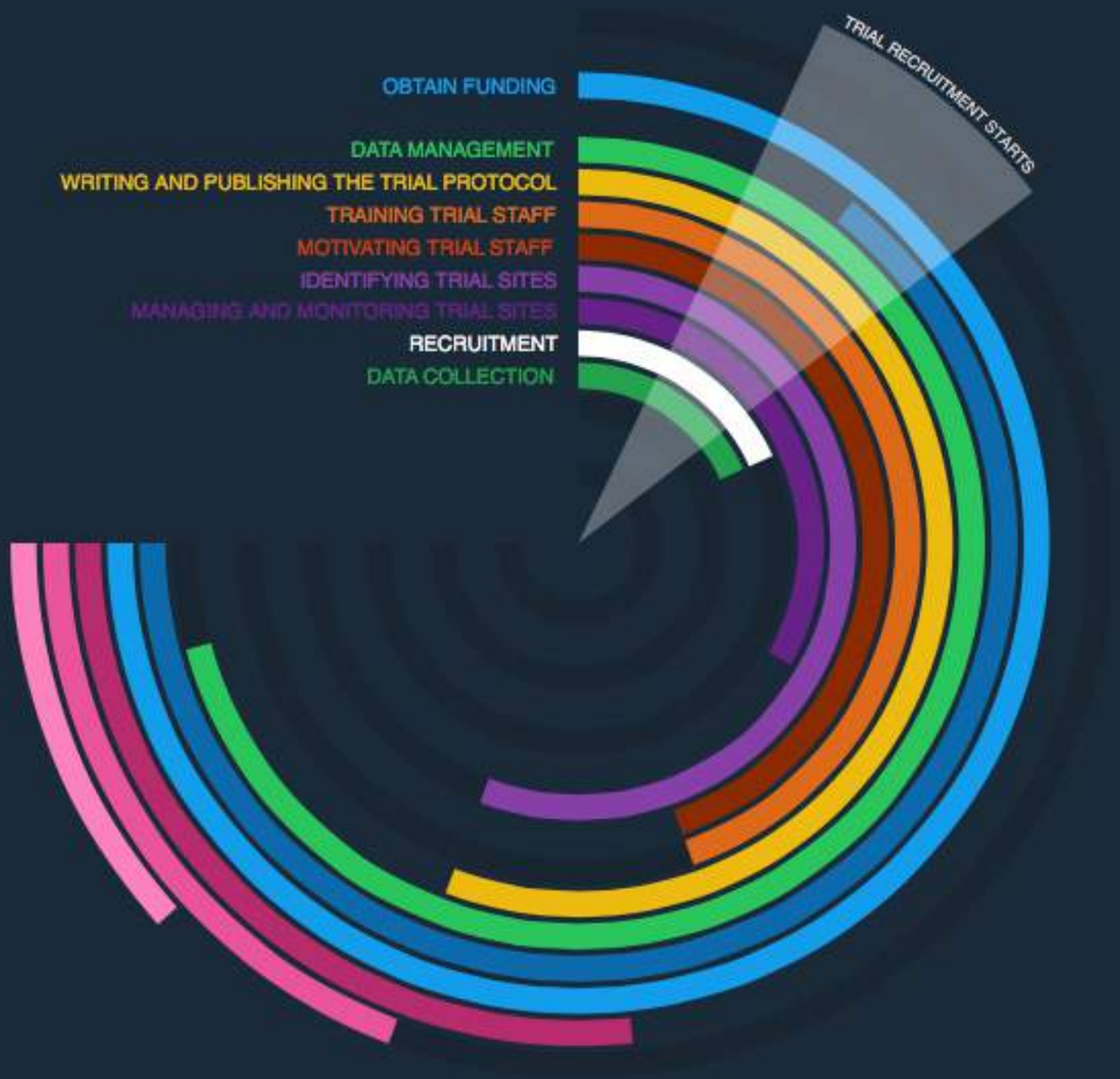
Dr Bronia Arnott @BroniaArnott 14 Oct
Peter Craig talking about reducing research waste - need for a robust approach to be more efficient #exetercomplex
Retweeted by Trial Forge
Joanna Crocker @joannacrocker 12 Oct
Experimenting with PPI: Could we? Should we? bit.ly/1jrRqrJ
Retweeted by Trial Forge
Iain Chalmers @iainchalmersTTi 11 Oct
100-year history of reporting guidelines by Doug Altman and Iveta Simera published in James Lind Library. equator-network.org/2015/10/09/a-h...
Retweeted by Trial Forge

Trial Forge - simple steps to a big change

Trial Forge in 5 steps

1. Identify discrete trial processes
2. Collate what is known (or not known) about each process
3. Suggest ways in which that process might be improved, or evidence gaps filled
4. Evaluate the use of that improvement
5. Disseminate the results to the people who need to know about them

https://s3-eu-west-1.amazonaws.com/bullorbear-static/trialforge/index.html



RECRUITMENT

x

TIP 1

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TIP 2

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TIP 3

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TIP 4

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TIP 5

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MORE INFO

TRIAL FORGE

HOME ABOUT WORKSHOP PATHWAY CONTACT

Back to Pathway

RECRUITMENT

RESOURCES

Choose Resource Type

Offering cash

September 18, 2015

Vestibulum ante ipsum primis in faucibus orci luctus et ultrices posuere cubilia Curae; Donec velit neque, auctor sit amet aliquam vel, ullamcorper...

Evidence

Opt-out rather than opt-in

September 18, 2015

Vestibulum ante ipsum primis in faucibus orci luctus et ultrices posuere cubilia Curae; Donec velit neque, auctor sit amet aliquam vel, ullamcorper...

Evidence

Telephone reminders to non-respondents

September 18, 2015

Vestibulum ante ipsum primis in faucibus orci luctus et ultrices posuere cubilia Curae; Donec velit neque, auctor sit amet aliquam vel, ullamcorper...

Evidence

The business approach 3

September 18, 2015

Vestibulum ante ipsum primis in faucibus orci luctus et ultrices posuere cubilia Curae; Donec velit neque, auctor sit amet aliquam vel, ullamcorper...

Evidence

Stuff you can use

S

Telephone reminders to non-respondents

September 18, 2015

Telephoning people who do not respond to mailed invitations to take part in a trial **probably increases** recruitment.

RATING

EVIDENCE

TRIALFORGE

Recruitment: Telephone reminders

– ***Telephoning people*** *who do not respond to mailed invitations to take part in a trial* ***probably increases*** *recruitment.*

How big is the effect?

Number recruited before:	30 participants per 100	50 participants per 100	70 participants per 100
Number recruited after:	**16 more per 100**	**16 more per 100**	**12 more per 100**
95% confidence interval	1 to 21 more	1 to 29 more	1 to 20 more

What do I need to use telephone reminders?

The intervention is **simple**: all you need is a telephone, a person to make calls and a list of numbers to call.

How much work is involved in using telephone reminders?

This is **uncertain**. If you are considering using telephone reminders and would like to help reduce the uncertainty about workload, email Collaborate@TrialForge.org.

Trial Forge demonstrators

- Design: matching design to intention
- Recruitment: how should we select sites for trials?
- Data collection: how much time do we spend collecting data?
- Studies within a trial (SWATs)

Design: PRECIS-2

Who am I designing my trial for and what have I done to make sure they don't have to dismiss my trial as irrelevant?

Kirsty Loudon, Stirling

Who are your users and what do they want?

Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, Zwarenstein M. The PRECIS-2 tool: designing trials that are fit for purpose. BMJ 2015; 350: h2147–7.

Design - PRECIS 2

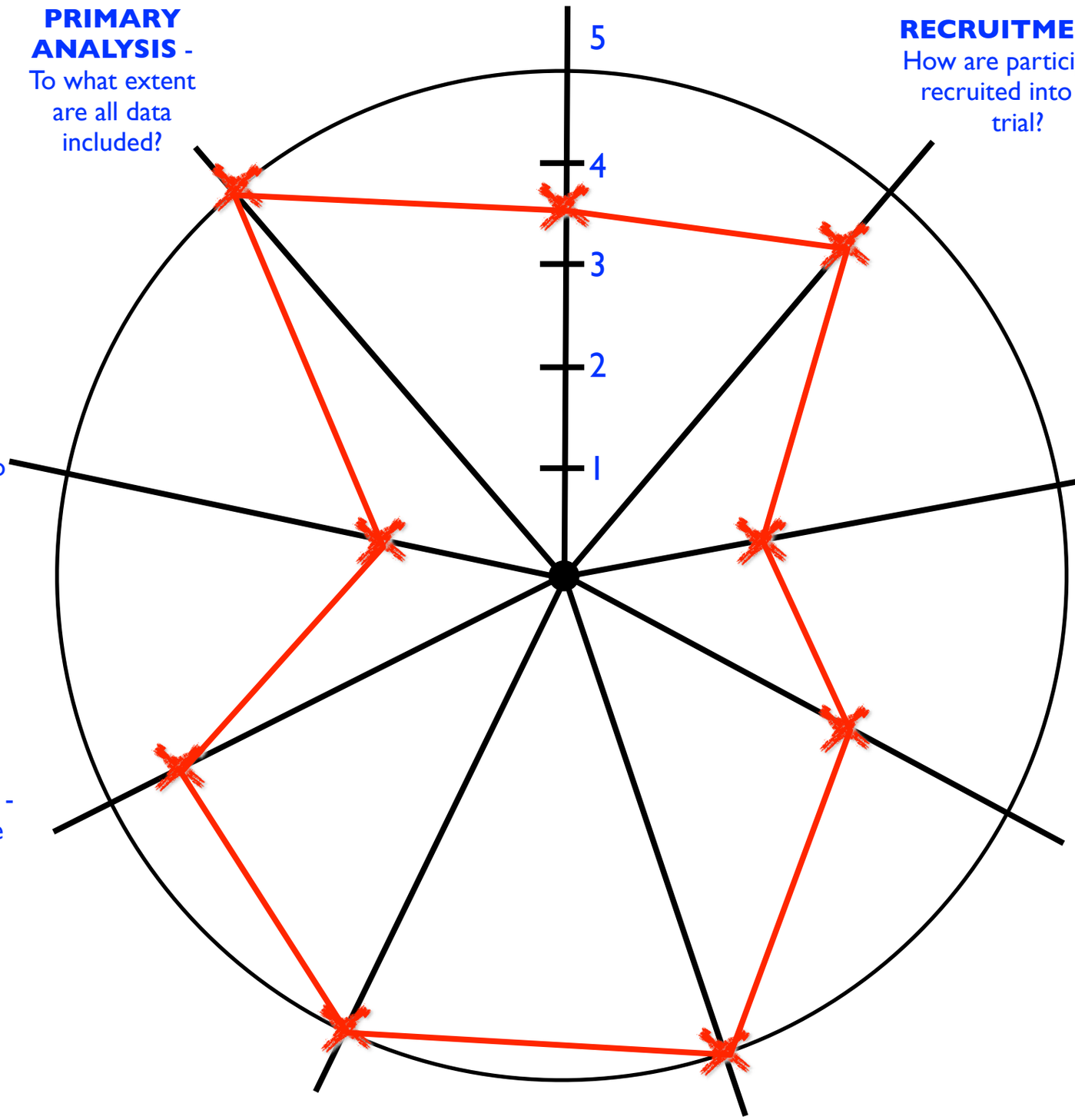
ELIGIBILITY -
Who is selected to participate in the trial?

PRIMARY ANALYSIS -
To what extent are all data included?

RECRUITMENT -
How are participants recruited into the trial?

PRIMARY OUTCOME -
How relevant is it to participants?

SETTING -
Where is the trial being done?



FOLLOW-UP -
How closely are participants followed-up?

ORGANISATION -
What expertise and resources are needed to deliver the intervention?

FLEXIBILITY: ADHERENCE -
What measures are in place to make sure participants adhere to the intervention?

FLEXIBILITY: DELIVERY -
How should the intervention be delivered?

RECRUITMENT: how to select sites?

- Most trials need to select several sites
- Many of these will fail to do what they are supposed to do (especially recruit)
- Evidence on how to best select sites is thin

Kirsty Shearer, Seonaidh Cotton, Anne Duncan, Hanne Bruhn
Aberdeen

Estimating Site Performance (ESP) study

Estimating Site Performance (ESP) Study Protocol

Sponsor

No sponsor required if ethics approval is obtained and only University staff involved.

Lead investigator

Dr Kirsty Shearer

Co-investigators

Prof Shaun Treweek, Dr S

Funding

No costs involved

Location

CHaRT, Health Science Bu

STUDY SUMMARY

Question asked – Is the
investing energy in when

Considered for entry – Tr

Populations – Trial mana

Outcome assessment –
predicted target b) what

Co-ordination – CHaRT, U

mating

formance

Study consent form

Please initial all boxes

g each box I agree that I have:

on sheet about the study (v1.0 20/10/2014)

discuss the study

rmation about the study

Information sheet on the ESP study

Background information

A large investment of public money is made by the UK each year to fund large multicentre clinical trials. Reviews have found that many (around half) of these studies will not recruit to target and have to either have extensions, revisions to the sample size (power of the study) or are closed, which essentially leaves the clinical question unanswered. There are many reasons that contribute to these failures. One of these is that some local sites just fail to perform as recruitment centres and never fulfil their predicted potential. A great amount of time, effort and cost is taken in setting up local recruitment centres around
trial's chief investigator as em
Alternatively local sites have be
without prior contact with the
Another route for attracting loc
approach the trial office. Regardl
be ideal to have a way to pote
involved in the trial (in this conte
words, is there a good way of ma
which are not?

The ESP study

CHaRT is a busy CTU with a large
local site set-up and are deeply ir
whether a site will go on to rec
predictions to actual recruitmen
their predictions. If we can der
recruitment success, then we can
invest in a site, abandon it, or n
This would enable energy to be
prevent it being wasted on sites t

We would like the TMs of studies
very short form about each site t
a 'good' or 'bad' site. This will h

ESP recruitment prediction form

Name of trial manager		Name of trial	
How long have you been a trial manager?		What CTU are you based at?	
Site visiting		Date of prediction	

What is the site's recruitment target?				
Which of the following as the site had? *Circle as many as necessary*	On site SIV	Teleconf SIV	Launch meeting	Other
What is the site status?	Opened for recruitment		Abandoned	
In your opinion, will this site recruit to its target on time?	Yes		No	
Why do you think this (for sites being opened)? **OR** Why was the site abandoned? *Please continue overleaf if needed*				

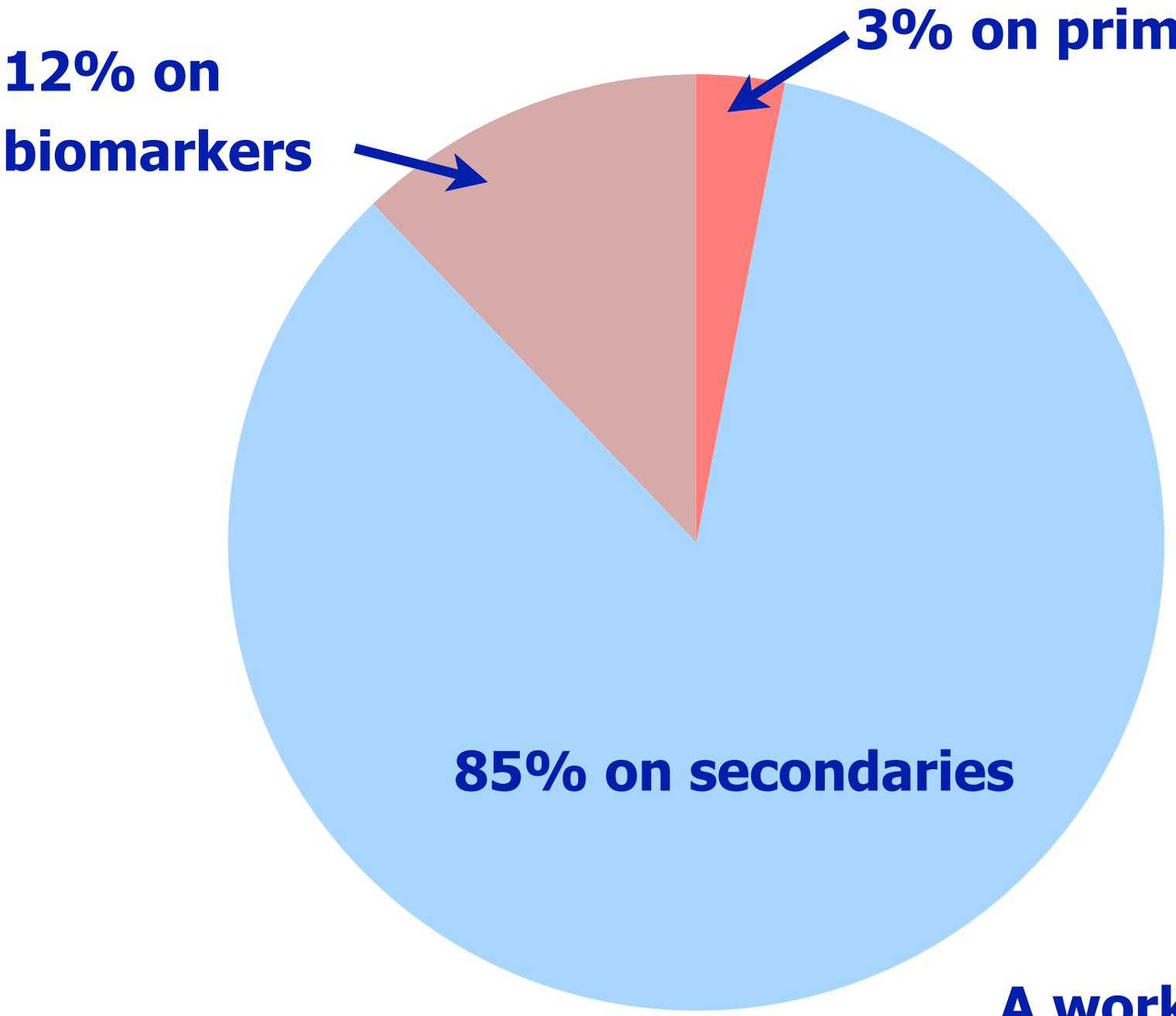
Data collection: time spent

Where do we invest our time when collecting outcome data?

Do we spend most of it on our most important outcomes?

Me, Aberdeen & David Pickles, Leeds

Example 2: data collection



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Filling evidence gaps: SWATs

Mike Clarke, Belfast

JOURNAL OF EVIDENCE-BASED MEDICINE

Journal of Evidence-Based Medicine ISSN 1756-5391

METHODOLOGY

SWAT 1: what effects do site visits by the principal investigator have on recruitment in a multicentre randomized trial?

Valerie Smith[1], Mike Clarke[2], Declan Devane[3], Cecily Begley[1], Gillian Shorter[4] and Lisa Maguire[2]

[1] School of Nursing and Midwifery, Trinity College Dublin, Ireland
[2] All-Ireland Hub for Trials Methodology Research, Queen's University Belfast, Northern Ireland
[3] School of Nursing and Midwifery, National University of Ireland Galway, Ireland
[4] All-Ireland Hub for Trials Methodology Research, University of Ulster, Northern Ireland

Keywords
Multicentre randomized trial; recruitment; study within a trial (SWAT).

Correspondence
Mike Clarke, All-Ireland Hub for Trials Methodology Research, Centre for Public Health Institute of Clinical Sciences, Block B, Queens University Belfast Royal Hospitals, Grosvenor Road, Belfast BT12 6BJ, Northern Ireland.
Tel: +44 (0)28 90635059;
Fax: +44 (0)28 90235900;
Email: m.clarke@qub.ac.uk

Received 21 July 2013; accepted for publication 23 July 2013.

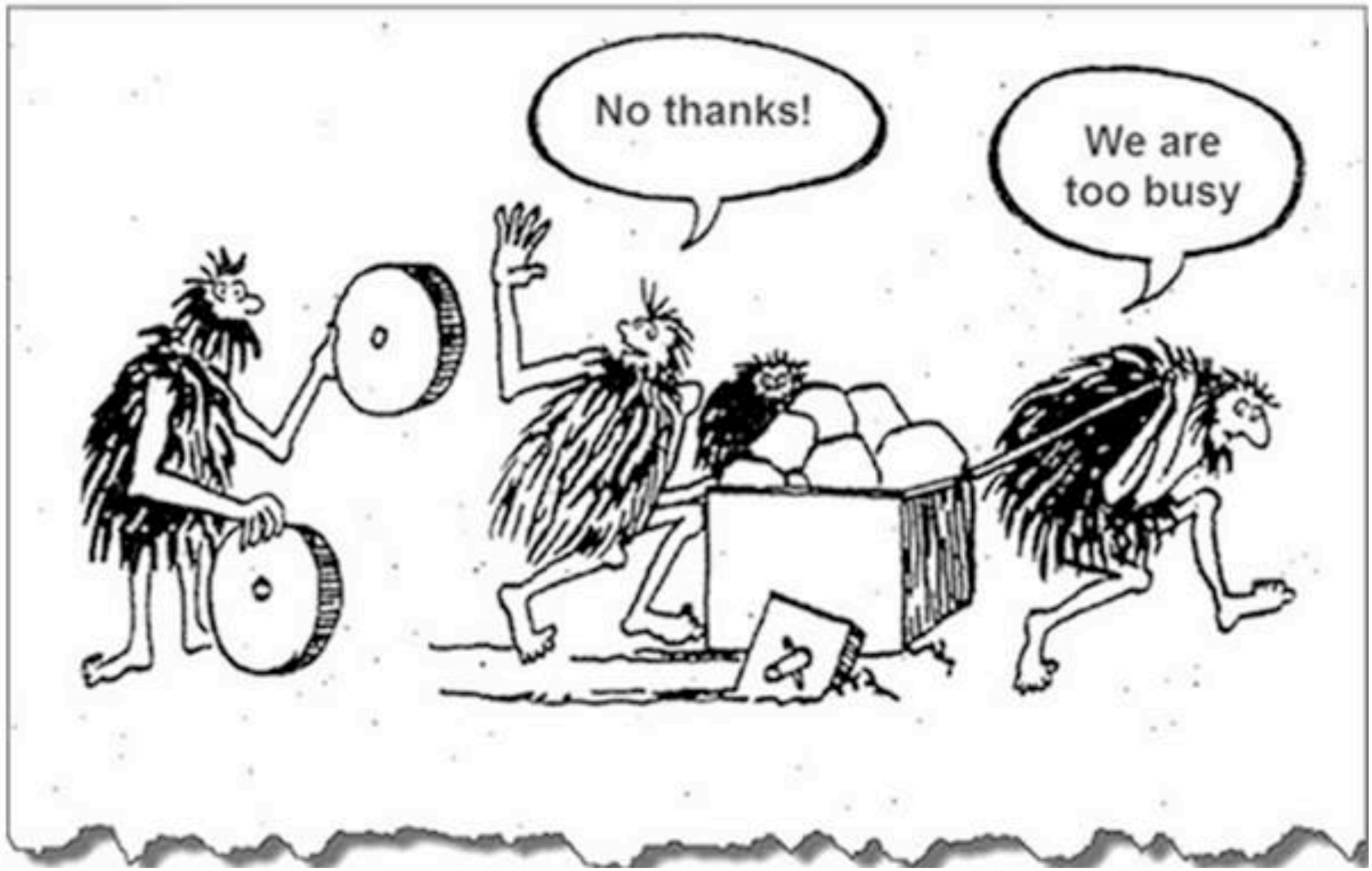
Abstract

The SWAT (Study Within A Trial) programme has been established to develop a series of studies that would embed research within research, so as to resolve uncertainties about the effects of different ways of designing, conducting, analyzing and interpreting evaluations of health and social care. It was described in an Education piece in the *Journal of Evidence-Based Medicine* in 2012. We have now prepared the first example of the design summary for a SWAT, using the template that will be used for other SWAT. This is presented in this article.

Summary

- To a large extent, we do trials the way we do because that's the way we do them.
- The chances are that we can do better than this through more collaboration and coordination.
- Through Trial Forge we want to move beyond saying how grim everything is and start working on solutions.
- Join up! (or at least follow @Trial_Forge..)

Time to consider new wheels..



Thank you!

TRIALFORGE

http://trialforge.org

Twitter: @Trial_Forge

HSRU is funded by the Chief Scientist Office of the Scottish Government Health and Social Care Directorates. The author accepts full responsibility for this talk.

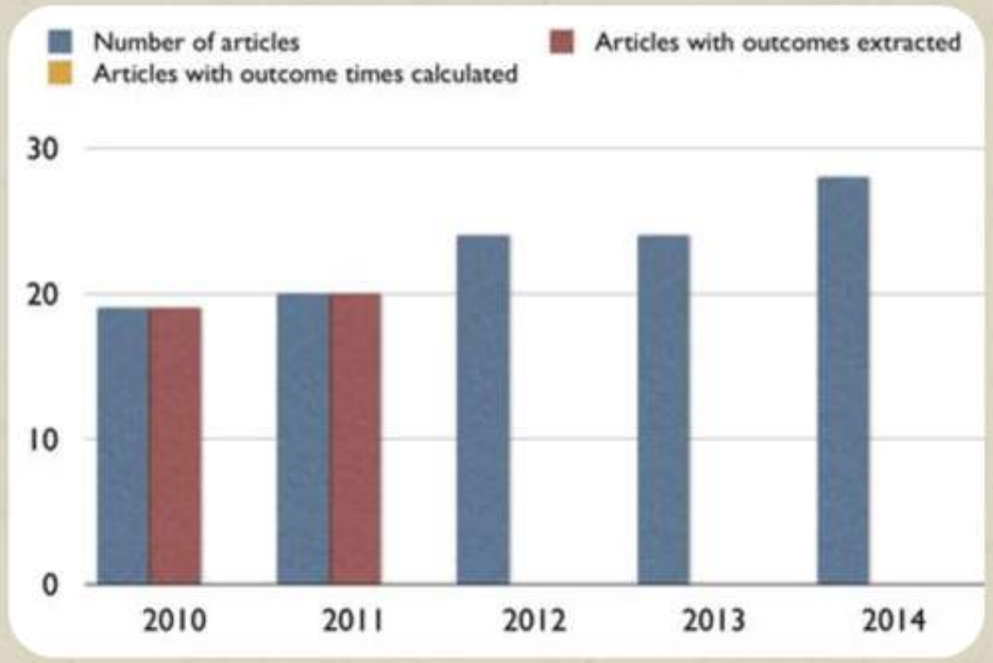
The PS: crowdsourcing methodology research?

How much time do we spend collecting trial outcome data?

How much time do we spend collecting trial outcome data?

Background

A primary outcome is the trial's most important outcome and usually there is just one, occasionally two. Trialists are less focused when it comes to secondary outcomes, which are by definition of less importance than the primary outcome. It would be perverse if trial participants and trial teams spent most of their time providing, collecting and managing data associated with outcomes of lesser importance. Since current estimates are that data management accounts for around a third of all time spent on trials [1], the consequences of this are not trivial. However, there are no data that explicitly compare the time spent collecting primary outcome data with the time spent collecting secondary outcome data. This is what we aim to do with this project.



What do we need?

We've randomly selected a bunch of 115 trials from 2010 – 2014 and we've extracted the primary and secondary outcomes for 2010 and 2011. What we need now is help extracting data for the three remaining years, together with help estimating the time taken to use each of the outcomes used in the trials. The work would be great experience for PhD or other students; indeed Alex Duthie, a student visiting Aberdeen from Australia, did all the data extraction so far.

What will you get?

The study will be published so all contributors will be authors or acknowledged, depending on the contribution. You'd be part of a new kind of project and, of course, you'd be helping to answer a question that we probably have a gut-feeling for but lack empirical data to support that feeling. Some concrete data would (we think) help us all to be a bit more efficient when selecting outcomes and committing our trial data management resources.

Created page, tweet on 4/4; response on 5/4; project taken on 10/4. Now part of an MSc project.

Protocol 2014: each measured twice

Primary outcome

We will assess depressive symptoms as a primary outcome of the present study using the short version geriatric depression scale GDS-15. Prevalence of depression, median of GDS-15, and the mean value of difference between baseline and three months later will be compared between the intervention group and the control group.

Secondary outcomes

As secondary outcomes, we will measure subjective and actigraph-measured sleep quality, sleepiness, glycated haemoglobin (HbA1c), fasting plasma glucose (FPG), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), body mass index (BMI), abdominal circumference, circadian rhythm of physical activity and wrist skin temperature, urinary melatonin metabolite, chronotype, post-illumination pupil response (PIPR), visual acuity, and subjective visual function.

Protocol 2014: each measured twice

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Secondary outcomes **17 measurements**

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Secondary outcomes **17 measurements** **276 full days**

As secondary outcomes, we will measure subjective and actigraph-measured sleep quality, sleepiness, glycated haemoglobin (HbA1c), fasting plasma glucose (FPG), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), body mass index (BMI), abdominal circumference, circadian rhythm of physical activity and wrist skin temperature, urinary melatonin metabolite, chronotype, post-illumination pupil response (PIPR), visual acuity, and subjective visual function.